


# The contribution of depressive symptoms to slowness of information processing in Relapsing Remitting Multiple Sclerosis

| | |
|---|---|
| Journal: | *Multiple Sclerosis Journal* |
| Manuscript ID | MSJ-16-0087.R1 |
| Manuscript Type: | Original Research Paper |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Lubrini, Genny; University Hospital La Paz, Neurology<br>Ríos Lago, Marcos; Beata Maria Ana Hospital, Brain Damage Service; UNED, Basic Psychology<br>Periañez, Jose A; Complutense University of Madrid, Basic Psychology II<br>Tallon Barranco, Antonio; University Hospital La Paz, Neurology<br>De Dios, Consuelo; University Hospital La Paz, Psychiatry<br>Fernandez-Fournier, Mireya; University Hospital La Paz, Neurology<br>Diez Tejedor, Exuperio; University Hospital La Paz, Neurology<br>Frank García, Ana; University Hospital La Paz, Neurology |
| Keywords: | Multiple sclerosis, Depression, Information Processing Speed, Reaction Time, Visual Search |
| Abstract: | Background: Slowness of information processing has been suggested as a fundamental factor modulating cognitive impairment in MS. However, the contribution of depressive symptoms (DS) to slowness remains unclear. One of the most accepted hypotheses on the impact of depression in the general population suggests that depression interferes only with tasks requiring high cognitive demands. However, no studies have investigated if the same pattern occurs in MS.<br>Objective: To determine the profile of the contribution of DS to slowness.<br>Methods: Four Reaction Time (RT) tasks requiring an increasing level of cognitive demands were administered to 35 Relapsing-Remitting MS patients with DS, 33 MS patients without DS, 17 depressed non-MS patients, and 27 controls.<br>Results: MS patients without DS obtained longer RTs than controls in all the tasks. On the contrary, depressed non-MS patients were slower than controls only in the most demanding task. Finally, MS patients with DS were slower than MS patients without DS not only in the most demanding task, but also in the task requiring a lower level of cognitive demands. |

| | |
|---|---|
| | Conclusion: The contribution of DS to slowness depends on the level of cognitive demands. However, its impact in MS is more deleterious than in the general population. |
| | |

# The contribution of depressive symptoms to slowness of information processing in Relapsing Remitting Multiple Sclerosis

**Lubrini G[1*], Periañez JA[2], Ríos-Lago M[3,4], Tallón Barranco A[1], De Dios C[5], Fernández-Fourier M[1], Diez Tejedor E[1], Frank García A[1]**

[1] Dep. of Neurology/La Paz University Hospital/Health Research Institute (IdiPAZ)/Autónoma University of Madrid, Madrid, Spain.

[2] Dep. of Basic Psychology II/Complutense University of Madrid, Madrid, Spain

[3] Brain Damage Service/Beata Maria Ana Hospital, Madrid, Spain.

[4] Dep. of Basic Psychology II/UNED, Madrid, Spain.

[5] Dep. of Psychiatry/La Paz University Hospital/Health Research Institute (IdiPAZ)/Autónoma University of Madrid, Madrid, Spain.

**Author for correspondence:**

*Genny Lubrini

Dep. of Neurology/La Paz University Hospital/Health Research Institute (IdiPAZ)/Autónoma University of Madrid.

Paseo de la Castellana 261, 28046 Madrid. Spain

Fax number: +34 913581403. Telephone number: +34 917277595

e-mail: genny.lubrini@hotmail.it

**Key words:** Depression, Information processing speed, Multiple Sclerosis, Neuropsychological assessment, Reaction Time, Visual Search.

**Abstract**

**Background**: Slowness of information processing has been suggested as a fundamental factor modulating cognitive impairment in MS. However, the contribution of depressive symptoms (DS) to slowness remains unclear. One of the most accepted hypotheses on the impact of depression in the general population suggests that depression interferes only with tasks requiring high cognitive demands. However, no studies have investigated if the same pattern occurs in MS.

**Objective:** To determine the profile of the contribution of DS to slowness.

**Methods:** Four Reaction Time (RT) tasks requiring an increasing level of cognitive demands were administered to 35 Relapsing-Remitting MS patients with DS, 33 MS patients without DS, 17 depressed non-MS patients, and 27 controls.

**Results:** MS patients without DS obtained longer RTs than controls in all the tasks. On the contrary, depressed non-MS patients were slower than controls only in the most demanding task. Finally, MS patients with DS were slower than MS patients without DS not only in the most demanding task, but also in the task requiring a lower level of cognitive demands.

**Conclusion:** The contribution of DS to slowness depends on the level of cognitive demands. However, its impact in MS is more deleterious than in the general population.

## 1. Introduction

Slowness of information processing represents one of the key cognitive deficits in MS patients.[1] The primacy of slowed processing has been formalized by DeLuca et al.[2] in their Relative Consequence Model, suggesting that cognitive impairment in MS might be a by-product of speed deficits. However, there is current debate regarding what role clinical variables such as depression play as contributing factors to slowness. Clarifying this point is of particular relevance given that depression is one of the most frequent psychiatric diagnoses in MS affecting between 27-54% of all patients.[3]

The impact of MS on processing speed has been largely documented.[4-6] However, only a few investigations have differentiated between depressed and non-depressed patients, studying the effect of MS on its own. Neuropsychological research has demonstrated that MS affects the performance of non-depressed patients in tasks involving attention, working memory, executive functions, and processing speed.[7-11]More ambitious studies using Reaction Time (RT) tasks have confirmed an impact of MS finding that non-depressed MS patients are slower than controls in all tasks irrespective of their complexity.[12,13]
On the other hand, different authors have compared the performance of depressed and non-depressed MS patients to isolate the impact of depression. Results suggest that depression

affects MS patient's performance by exacerbating slowness due to the disease itself.[8,11,14] However, existing data do not permit to establish to what extent speed deficits are caused by depression. Studies in the general population have attempted to clarify whether depression affects cognitive performance. One of the most accepted hypotheses suggests that depression interferes only with highly effortful tasks requiring a great deal of attentional capacity ("The cognitive effort hypothesis").[15,16] Until now, only one study has considered if the impact of depression in MS follows the same pattern. A study assessing performance in high and low capacity cognitive tasks revealed that depressed MS patients performed significantly worse than non-depressed MS patients on speeded capacity-demanding attentional measures but not on any tasks with low capacity demands.[17] However, this study analysed the cognitive effort in a dichotomous way without establishing a continuum of tasks requiring an increasing degree of cognitive demand, which could help to determine the level of cognitive demands that exceeds depressed patients available resources. For this purpose, evidences from depression in the general population have highlighted the usefulness of RT based paradigms where automatic and effortful processing can be manipulated within comparable tasks,[18] an approach that has no yet been applied to MS.

The aim of the present study was to clarify the relative contribution of MS and depressive symptoms (DS) to slowness of processing exhibited by MS patients. With this purpose, a comprehensive set of RT tasks with an increasing level of cognitive demands was administered to two Relapsing Remitting MS patient groups differing in terms of presence or absence of DS, a group of depressed patients without MS, and a group of healthy controls. Based on findings in the literature, two hypotheses were formulated. Firstly, it was hypothesized that MS patients without DS would obtain slower RT than controls in all tasks. Secondly, MS patients with DS were expected to be slower than MS patients without DS. However, according to the cognitive effort hypothesis, differences between groups were expected to emerge as the cognitive load increased.

## 2. Method

### *2.1. Participants*

Sixty-eight MS patients were divided in two groups according to the presence of DS defined by a cut-off score≥13 in the Spanish version of the Beck Depression Inventory (BDI).[19-22] Thirty-three MS patients were included in the group without DS and 35 in the group with DS. As the validity of the BDI for assessing depression in MS is questionable due to the overlap of MS symptoms and vegetative symptoms of depression, a second classification was also performed considering the cut-off score of 8 in the modified version of the BDI proposed by Strober and Arnett.[23,24] This new criterion did not change the original classification. Seventeen depressed patients without MS and 27 non-depressed healthy controls also participated in this study. Depressed patients had a clinical diagnosis of mild or moderate major depressive disorder according to DSM-5 [25] criteria and a BDI score≥13 at the time of testing. Eligibility criteria for all participants included no history of alcohol or drug abuse, nervous system disorder (other than MS) or premorbid history of learning disabilities, and absence of motor or visual impairment that might interfere with testing. Inclusion criteria for MS patients were: diagnosis of MS according to McDonald's criteria;[26] a current diagnosis of a Relapsing Remitting course; score on the Expanded Disability Status Scale<6 (EDSS);[27] and absence of relapses or treatment with prednisolone in the month prior to testing. Demographic and clinical features are shown in Table 1. All participants were right-handed. The study was approved by the Ethics Committee of the University Hospital La Paz. Participants signed the informed consent according to the Declaration of Helsinki.

*****************************

**Table 1 about here**

*****************************

*2.2. Experimental tasks and procedures*

Participants were examined with four RT tasks designed to target skills ranging from basic reaction speed and simple perceptual-motor demands to more complex cognitive processes (Fig.1). All testing was performed using a PC with a 17-in. monitor controlled by Presentation® software (http://www.neurobs.com). All stimuli were white displayed on a black screen. Participants were seated approximately 60 cm from the screen and instructed to keep looking at the fixation point in the centre of the screen. The order of task presentation was counterbalanced across participants. In all RT tasks, both speed (average RTs from correct trials) and accuracy (percentage of correct responses) were measured. The two first responses from each task were discarded for the analysis.

*Simple Reaction Time (SRT):* In this task, based on the Simple RT task of the Computerized Tests of Information Processing,[12] participants pressed the left button of the mouse with the right index finger as quickly as possible when the stimulus "+" appeared in the centre of the screen (size 2×2 cm). The task consisted of 50 trials with a total duration of 2-3 min.

*Simple Reaction Time-Sustained Attention to Response Task (SRT-SART):* In this task, derived from the SART paradigm,[28] participants pressed the left button of the mouse with the right index finger whenever a stimulus (a digit between 1 and 9) appeared in the centre of the screen, but not pressed the button if the digit shown was number 3. Digits were presented in Arial font in one of three randomly allocated font sizes (40, 70 or 100 points, with a height varying between 12mm and 29mm). This enhanced the demands of processing the numerical value rather than simply setting a search template for some peripheral feature of the No Go stimulus. The task consisted of 189 trials (21 of them were No Go trials). A pause was set after trial 94. The total task duration was approximately 4 min. No Go trials were distributed in a pre-fixed semi-random fashion throughout the task, ensuring that there were between 5 and 17 Go trials between two No Go trials.

*Choice Reaction Time (CRT):* In this task based in the Visual Choice Reaction Time task by Chiaravalloti et al.,[29] participants pressed the left or the right button of the mouse with the index finger of the left or the right hand every time a square or a circle, respectively, appeared in the centre of the screen. All stimuli were the same size (4×4 cm). The task consisted of 80 trials with an approximate duration of 2 min. 50 sec. The order of stimuli presentation was randomised but remained constant among participants.

*Choice Reaction Time-Search (CRT-Search):* In this task, derived from one of Neisser's paradigms,[30] participants pressed the left button of the mouse with the left index finger whenever the presented stimulus, consisting of a string of 6 letters, included the letter "Z". If this was not the case, they had to press the right button with the right index finger. Stimuli were presented in Arial font with size 4.5×2.5 cm. The task consisted of 128 trials. Each trial presented a stimulus that remained on the screen until the subject responded, for a maximum of 4000 ms. The order of stimuli presentation was randomized but remained constant among participants. The task duration varied between 5-8 min. On target trials, the letter "Z" appeared in one of the four central positions of the letter string with equal frequency but never in the first or in the sixth extreme positions to prevent interference inhomogeneities due to targets flanked by a single distractor.

****************************

**Figure 1 about here**

****************************

*2.3. Analysis*

Group differences for demographic and clinical variables (sex, age, education, disease duration, EDSS, and BDI score) were determined by means of *t*-tests or Chi-square tests. Four two-way ANOVAs with repeated measures Task by Group (MS without DS Vs

Controls, Depressed Vs Controls, MS with DS Vs MS without DS; MS with DS Vs Depressed) were used to assess differences between groups in RTs and percentage of correct responses. A significance level of $p<0.05$ was adopted for all analyses. A Bonferroni-corrected significance level of $p<0.05$ was adopted for tests involving multiple comparisons. Analyses were performed using SPSS v17.0.

**3. Results**

*3.1 Demographics*

No differences were found between depressed patients and controls in sex ($\chi2(1)=2$; $p=0.658$), age ($t(42)=2$; $p=0.063$) or education ($t(42)=-0.86$; $p=0.393$). As expected, depressed patients obtained higher BDI scores than controls ($t(42)=12.35$; $p<0.001$). MS patients without DS did not differ from controls in sex ($\chi2(1)=0.041$; $p=0.84$), age ($t(58)=0.6$; $p=0.602$), education ($t(58)=-1.9$; $p=0.06$), or BDI score ($t(58)=1.54$; $p=0.129$). The two groups of MS patients did not differ in any demographic or clinical variables ($p>0.18$ in all cases; see Table 1), except for BDI score ($p<0.001$). MS patients with DS did not differ from depressed patients in sex ($\chi2(1)=0.621$; $p=0.43$), age ($t(50)=-1.1$; $p=0.296$), education ($t(50)=-1.2$; $p=0.241$), or BDI score ($t(50)=0.2$; $p=0.183$).

*3.2 Reaction Time (RTs)*

The ANOVA comparing RTs of MS patients without DS and controls revealed a main effect of Group ($F(1,58)=12.7$; $p=0.001$), showing that MS patients had slower RTs. There was also a main Task effect ($F(2,80)=355$; $p<0.001$), indicating a progressive increase of RTs as the tasks became more complex ($p<0.001$ in all cases). A significant Group x Task interaction ($F(2,80)=7.8$; $p=0.003$) revealed that, although differences between groups progressively increased with the augmentation of tasks cognitive demands, a much greater separation in their performance appears in the CRT-Search task ($p<0.044$ in all cases; Fig.2).

The ANOVA comparing RTs of depressed patients and controls revealed a main effect of Group ($F(1,42)=4.6$; $p=0.038$), showing that depressed patients had slower RTs. There was also a main Task effect ($F(2,70)=547.7$; $p<0.001$), indicating a progressive increase of RTs as the tasks became more complex ($p<0.001$ in all cases). A significant Group x Task interaction ($F(2,70)=8.8$; $p=0.001$) revealed that differences emerged only in the CRT-Search task ($p=0.003$; Fig.3).

The ANOVA comparing RTs of MS patients with and without DS revealed a main effect of

Group (F(1,66)=4.6; p=0.036), showing that MS patients with DS had slower RTs. There was also a main Task effect (F(2,100)=356.1; p<0.001), indicating a progressive increase of RTs as the tasks became more complex (p<0.001 in all cases). A significant Group x Task interaction (F(2,100)=5.9; p=0.008; Fig.3) revealed that differences emerged only in the CRT and CRT-Search tasks (p=0.024 and p=0.017, respectively; Fig. 4).

The ANOVA comparing RTs of MS patients with DS and depressed patients revealed a main effect of Group (F(1,50)=5.2; p=0.026), showing that MS patients with DS had slower RTs. There was also a main Task effect (F(2,78)=256.1; p<0.001), indicating a progressive increase of RTs as the tasks became more complex (p<0.001 in all cases). A significant Group x Task interaction (F(2,78)=5.3; p=0.012; Fig.5) revealed that differences between groups emerged in the CRT and CRT-Search tasks (p=0.05 and p=0.014, respectively; Fig.5).

*****************************************

**Figures 2, 3, 4, and 5 about here**

*****************************************

*3.3 Accuracy*

All RT tasks were performed very efficiently (Table 2). In the ANOVAs with the percentage of correct responses, the main effect of Task was significant in all the comparisons ($p<0.001$). Post-hoc analyses revealed that the percentage of correct responses was greater for the SRT than for the CRT task in all cases ($p<0.003$), greater for the CRT-Search than for the CRT task ($p<0.023$), and greater for the TRS-SART than for the CRT task ($p<0.001$). The percentage of correct responses was higher in the SRT than in the CRT-Search task when comparing depressed patients and controls ($p=0.047$), and MS patients without DS and controls ($p=0.026$). The percentage of correct responses was higher in the SRT than in the SRT-SART task when comparing MS patients without DS and controls ($p=0.033$). No other differences were significant ($p>0.143$ in all cases). The main effect of Group reached significance only in the comparison between MS patients with DS and Depressed patients ($F(1,50)=4.3$; $p=0.044$), where MS patients were less accurate. The Group by Task interaction was not significant in any comparison ($p>0.198$ in all cases).

*****************************

**Table 2 about here**

*****************************

## 4. Discussion

The present study investigates the relative contribution of MS and DS to information processing deficits exhibited by MS patients. According to prior evidence, it was hypothesized that both MS and DS might play a role in slowed information processing speed in MS.[10,17] However, two different patterns of speed deficits were expected to emerge in MS patients with and without DS.

In order to isolate the impact of MS on processing speed, the performance of MS patients without DS was compared with a group of controls in different RT tasks requiring increasing cognitive demands. Results showed that patients were slower than controls in all RT tasks. This finding agrees with previous studies which report that the cognitive slowing that accompanies MS patients is widespread rather than task specific.[1,31,32] However, while differences between groups seem to remain quite constant in the first 3 tasks, a greater separation in their performance appears in the CRT-Search task. This task is considered the most complex as it requires, in addition to the choice procedure implied in the previous task of the continuum, the participation of attentional processes like interference control and visual search. Ulterior analyses should be performed in order to find which of these cognitive processes are responsible for the inordinate increase of RTs in this MS group.

The impact of depression on the general population was studied comparing performance of depressed patients and controls. Depressed patients obtained slower RT than controls only in the most complex task. This result supports the cognitive effort hypothesis which states that depression affects tasks requiring effortful information processing, but not those implying more automatic processing.[15,16]

In order to isolate the impact that DS had on processing speed in MS patients, the performance of MS patients with and without DS was compared. Patients with DS performed as well as those without DS in SRT and SRT-SART tasks but obtained a deficient performance in both CRT tasks. This agrees with previous findings suggesting that DS in MS patients has an impact on processing speed, exacerbating the slowness caused by MS.[17] Moreover, there was support for a specific effect of DS on effortful processing, rather than causing a widespread retardation. The present data extend previous work by providing the possibility to specify the level within the continuum from low to high cognitive demands where the impact of DS on processing speed in MS patients emerges. In this sense, the decision-making component involved in CRT tasks could be the factor exceeding MS patients' with DS available resources.[33]

The manipulation of the level of cognitive effort within comparable tasks allowed determining if the impact of DS on processing speed in MS is different to that of the general population. In fact, contrary to depressed patients without MS, MS patients with DS obtained a deficient performance not only in the most complex task but also in the previous one in the continuum (CRT task). Thus, DS seem to have a more deleterious effect in MS patients than in the general population. We speculate that the compounding effect of MS and DS leads to failure at tasks with lower cognitive demands than depression alone. The combined effect of MS and DS with respect to the impact of depression alone was further explored comparing MS patients with DS and depressed patients. Results revealed that MS patients with DS obtained slower RTs than depressed patients in the CRT and CRT-Search tasks, suggesting that presenting DS and having MS is more deleterious than just being depressed. Although differences did not emerge in the SRT and SRT-SART tasks, this null result was probably due to the small sample of depressed patients, as the magnitude of the difference was actually fairly large (Fig.5). Thus, as the impact of depression alone emerged only in the most complex task, the compounding effect of EM and DS seems to be widespread, affecting patients' performance in all the tasks although more steeply in the 2 most complex ones.

All RT tasks were performed very efficiently. Differences between groups in accuracy approached significance when comparing MS patients with DS and depressed patients. However, accuracy itself was high, with mean percentages of correct responses varying between 90% and 98%. Accordingly, and in line with prior MS investigations, the impact of both DS and MS on patients' performance seemed to be mainly restricted to processing speed with performance accuracy relatively spared.[12,18]

When interpreting the results, medication effects should be taken into account. Although we could not rule out the effect of medication in this study, most patients in both depressed groups were taking newer types of antidepressants, known to have less effect on cognition.[34]

This study is not exception in having limitations. First, the selection of MS patients with or without DS was based on a self-reported questionnaire cut-off rather than on a diagnostic interview. Second, the decision to include a homogeneous sample of MS patients with a relapsing remitting form of the disease restricts the generalizability of the results only to patients with this form of MS. Third, the sample sizes were relatively small, particularly for the depressed group; although significant effects were observed, the reliability of the findings should be explored in future research.

In summary, the results of the present study highlight that processing speed deficits of MS patients with DS depend on task cognitive demands. In fact, MS entirely accounts for deficits in less demanding tasks while, in tasks with a higher level of cognitive load, DS exacerbate the slowness caused by MS.

**Acknowledgements**

We want to thank all the MS patients and healthy participants who voluntarily and generously took part in the study.

**Conflict of interest statement**

The authors declare that there is no conflict of interest.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**References**

**1.** Kail R. Speed of information processing in patients with multiple sclerosis. *J Clin Exp Neuropsychol* 1998; 20: 98–106.

**2.** DeLuca J, Chelune GJ, Tulsky DS, et al. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *J Clin Exp Neuropsychol* 2004; 26(4): 550–562.

**3.** Feinstein A, Magalhaes S, Richard JF, et al. The link between multiple sclerosis and depression. *Nat Rev Neurol* 2014; 10(9): 507-17.

**4.** Denney DR, Gallagher KS and Lynch SG. Deficits in processing speed in patients with multiple sclerosis: evidence from explicit and covert measures. *Arch Clin Neuropsychol* 2011; 26(2): 110-119.

**5.** Macniven JA, Davis C, Ho MY, et al. Stroop performance in multiple sclerosis: Information processing, selective attention, or executive functioning? *J Int Neuropsychol Soc* 2008; 14: 805-814.

**6.** Van Schependom J, D'hooghe MB, Cleynhens K, et al. Reduced information processing speed as primum movens for cognitive decline in MS. *Mult Scler* 2015; 21(1): 83-91.

**7.** Arnett PA, Higginson CI, Voss WD, et al. Depression in multiple sclerosis: relationship to working memory capacity. *Neuropsychology* 1999; 13(4): 546-556.

**8.** Demaree HA, Gaudino E and DeLuca J. The relationship between depressive symptoms and cognitive dysfunction in multiple sclerosis. *Cogn Neuropsychiatry* 2003; 8(3): 161-171.

**9.** Denney DR, Sworowski LA and Lynch SG. Cognitive impairment in three subtypes of multiple sclerosis. *Arch Clin Neuropsychol* 2005; 20: 967-981.

**10.** Diamond BJ, Johnson SK, Kaufman M, et al. Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Arch Clin Neuropsychol* 2008; 23(2): 189-199.

**11**. Lubrini G, Perianez JA, Rios-Lago M, et al. Processing speed in relapsing-remitting multiple sclerosis: the role played by the depressive symptoms. *Rev Neurol* 2012; 16; 55(10): 585-592.

**12**. Reicker LI, Tombaugh TN, Walker L, et al. Reaction time: An alternative method for assessing the effects of multiple sclerosis on information processing speed. *Arch Clin Neuropsychol* 2007; 22: 655-664.

**13**. Ishigami Y, Fisk JD, Wojtowicz M, et al. Repeated measurement of the attention components of patients with multiple sclerosis using the Attention Network Test-Interaction (ANT-I): stability, isolability, robustness, and reliability. *J Neurosci Methods* 2013; 30; 216(1): 1-9.

**14**. Arnett PA, Higginson CI and Randolph JJ. Depression in multiple sclerosis: relationship to planning ability. *J Int Neuropsychol Soc* 2001; 7(6): 665-674.

**15**. Hammar A. Automatic and effortful information processing in unipolar major depression. *Scand J Psychol* 2003; 44(5): 409-13.

**16**. Hartlage S, Alloy LB, Vazquez C, et al. Automatic and effortful processing in depression. *Psychol Bull* 1993; 113: 247-278.

**17.** Arnett PA, Higginson CI, Voss WD, et al. Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning. *Neuropsychology* 1999; 13(3): 434-346.

**18**. Hammar A, Lund A and Hugdahl K. Selective impairment in effortful information processing in major depression. *J Int Neuropsychol Soc* 2003; 9(6): 954–959.

**19**. Beck AT and Steer RA. *Beck Depression Inventory: Manual*. New York: Psychological Corporation, 1987.

**20**. Sanz J and Vázquez C. Reliability, validity, and normative data of the Beck Depression Inventory. *Psicothema* 1998; 10(2): 303-318.

**21**. Lasa L, Ayuso-Mateos JL, Vazquez-Barquero JL, et al. The use of the beck depression inventory to screen for depression in the general population: a preliminary analysis. *J Affect Disord* 2000; 57: 261–265.

**22**. Stoquart-Elsankari S, Bottin C, Roussel-Pieronne M, et al. Motor and cognitive slowing in multiple sclerosis: an attentional deficit? *Clin Neurol Neurosurg* 2010; 112(3): 226-232.

**23**. Strober LB and Arnett PA. Assessment of depression in multiple sclerosis: development of a "trunk and branch" model. *Clin Neuropsychol* 2010; 24(7): 1146-1166.

**24**. Strober LB and Arnett PA. Depression in multiple sclerosis: The utility of common self-report instruments and development of a disease-specific measure. *J Clin Exp Neuropsychol* 2015; 37(7): 722-732.

**25.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th ed. Washington, D.C: American Psychiatric Association, 2013.

**26**. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58(6): 840-846.

**27.** Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-1452.

**28**. Robertson IH, Manly T, Andrade J, et al. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia* 1997; 35(6): 747-758.

**29**. Chiaravalloti ND, Chistodoulou C, Demaree HA, et al. Differentiating simple versus complex processing speed: Influence on new learning and memory performance. *J Clin Exp*

*Neuropsychol* 2003; 25: 489-501.

**30**. Neisser, U. Visual search. *Sci Am* 1964; 210(6): 94-102.

**31**. Kujala P, Portin R, Revonsuo A, et al. Automatic and controlled information processing in multiple sclerosis. *Brain* 1994; 117: 1115–1126.

**32**. De Sonneville LM, Boringa JB, Reuling IE, et al. Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia* 2002; 40: 1751–1765.

**33.** Thomas P, Goudemand M and Rousseaux M. Attentional resources in major depression. *Eur Arch Psychiatry Clin Neurosci* 1999; 249(2): 79-85.

**34**. Peretti S, Judge R and Hindmarch I. Safety and tolerability considerations: Tricyclic antidepressants vs. selective serotonin reuptake inhibitors. *Acta Psychiatr Scand Suppl* 2000; 403: 17–25.

## TABLES

**Table 1.** Means (S.D.) of demographic and clinical data from participants.

| | MS with DS | MS without DS | Depressed | Healthy Controls |
|---|---|---|---|---|
| N (male) | 35 (12) | 33 (9) | 17 (4) | 27 (8) |
| Age in years | 42.3 (8) | 40.5 (8) | 44.8 (7.8) | 39.2 (10.2) |
| Education in years | 13.2 (3.8) | 13.7 (3.3) | 14.5 (3.5) | 15.5 (4.2) |
| BDI score | 23.4 (7.2) | 6 (2.5) | 26.4 (8.1) | 4.9 (3.3) |
| EDSS | 2.6 (1.6) | 2.1 (1.6) | - | - |
| MS disease duration in months | 132.6 (98.4) | 119.6 (69) | - | - |

S.D.: Standard Deviation; DS: Depressive Symptoms; BDI: Beck Depression Inventory; EDSS: Expanded Disability Status Scale.

**TABLES**

**Table 2.** Means (S.D.) of Reaction Times (RT) and percent of correct responses (% correct) for the RT tasks in the four groups: MS patients with depressive symptoms, MS patients without depressive symptoms, Depressed patients, and Healthy Controls.

| | | MS with DS | MS without DS | Depressed | Healthy Controls |
|---|---|---|---|---|---|
| SRT | RT ms | 346.5 (139.6) | 315.1 (58.8) | 283.4 (40.2) | 282.3 (50.1) |
| | % correct | 96.4 (9.7) | 97.2 (4.2) | 98 (2.8) | 97.7 (2.8) |
| SRT-SART | RT ms | 401.8 (87.6) | 390.2 (70.5) | 366.8 (45.6) | 350.2 (55) |
| | % correct | 95.1 (3.3) | 95.3 (3.5) | 97 (1.2) | 96.7 (3.9) |
| CRT | RT ms | 555 (198.9) | 469 (81.7) | 456 (61.7) | 428.5 (67.6) |
| | % correct | 89.8 (7.6) | 87.7 (16.6) | 94.5 (5.1) | 93 (8.9) |
| CRT-Search | RT ms | 957 (308.4) | 804.6 (186.7) | 762 (98.1) | 655.3 (115.7) |
| | % correct | 94.2 (4.9) | 95.5 (3.2) | 96.4 (3.1) | 96.2 (3.9) |

S.D.: Standard Deviation; DS: Depressive symptoms; SRT: Simple Reaction Time task; SRT-SART: Simple Reaction Time-SART task; CRT: Choice Reaction Time task; CRT-Search: Choice Reaction Time-Search task.

## FIGURE LEGENDS

**Figure 1.** The figure illustrates an example of stimuli sequence of each RT task. In the SRT task participants were instructed to press a button as quickly as possible when the stimulus "+" appeared in the screen. In the SRT-SART task participants had to press a button whenever a digit between 1 and 9 appeared in the screen, except when the stimulus was the number 3 (No Go). In CRT task participants had to press the left or the right button every time a square or a circle appeared in the screen, respectively. In the CRT-Search task, participants had to press the left button when a stimulus consisting of a string of 6 letters included the letter "Z"; otherwise, they had to press the right button. Inter-Stimulus Interval (ISI) and stimulus duration (Stim. Duration) in each task are specified.

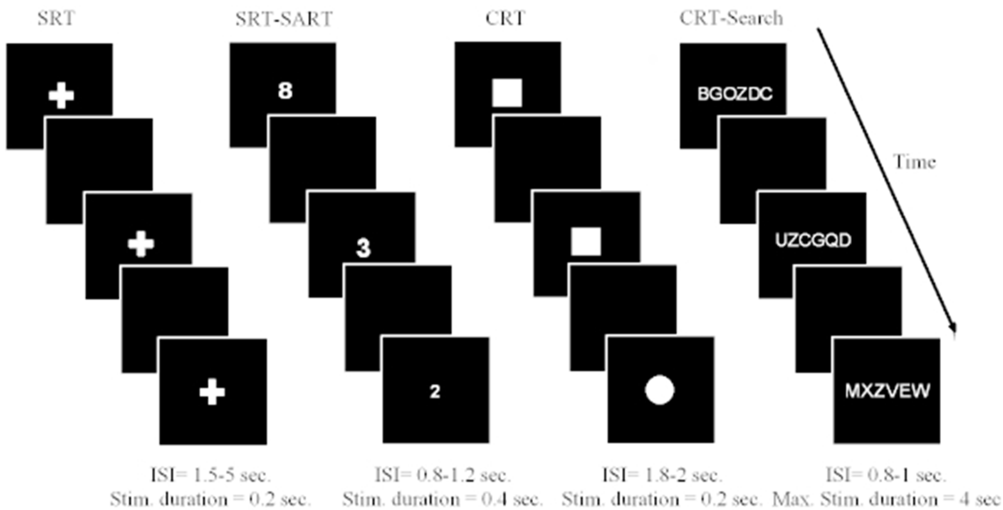
**Figure 2.** Comparison between reaction times (ms) of MS without depressive symptoms and Healthy Control groups. DS: Depressive symptoms; SRT: Simple Reaction Time task; SRT-SART: Simple Reaction Time-SART task; CRT: Choice Reaction Time task; CRT-Search: Choice Reaction Time-Search task (* $p < 0.05$; ** $p < 0.01$).

**Figure 3**. Comparison between reaction times (ms) of Depressed and Healthy Control groups. SRT: Simple Reaction Time task; SRT-SART: Simple Reaction Time-SART task; CRT: Choice Reaction Time task; CRT-Search: Choice Reaction Time-Search task (** $p < 0.05$).

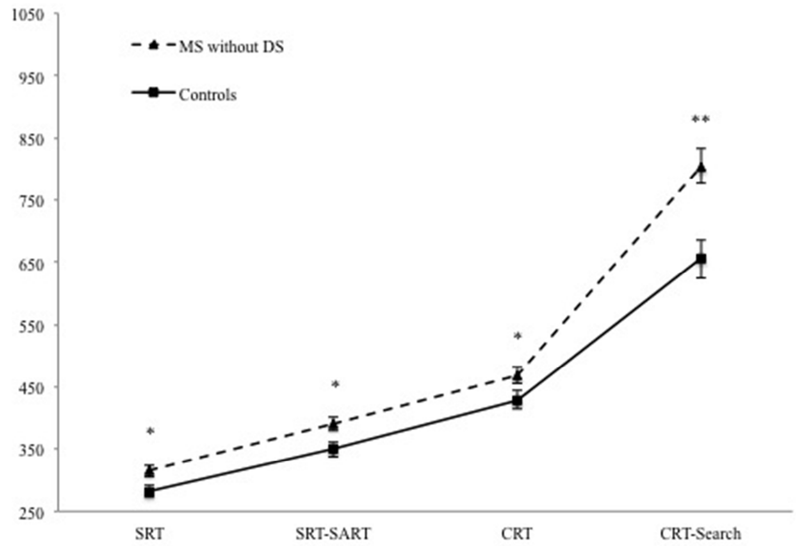
**Figure 4.** Comparison between reaction times (ms) of MS with depressive symptoms and MS without depressive symptoms groups. DS: Depressive symptoms; SRT: Simple Reaction Time task; SRT-SART: Simple Reaction Time-SART task; CRT: Choice

Reaction Time task; CRT-Search: Choice Reaction Time-Search task (* $p < 0.05$).

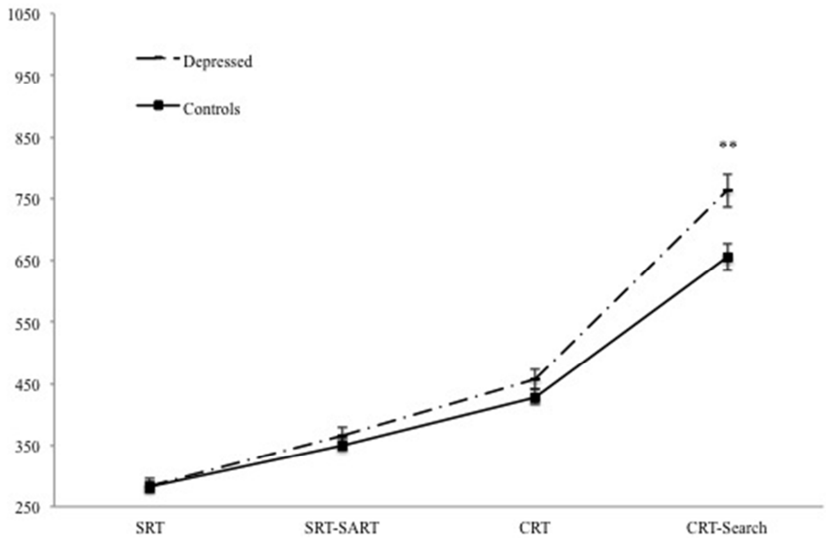
Figure 5. Comparison between reaction times (ms) of MS with depressive symptoms and depressed groups. DS: Depressive symptoms; SRT: Simple Reaction Time task; SRT-SART: Simple Reaction Time-SART task; CRT: Choice Reaction Time task; CRT-Search: Choice Reaction Time-Search task (* $p < 0.05$).



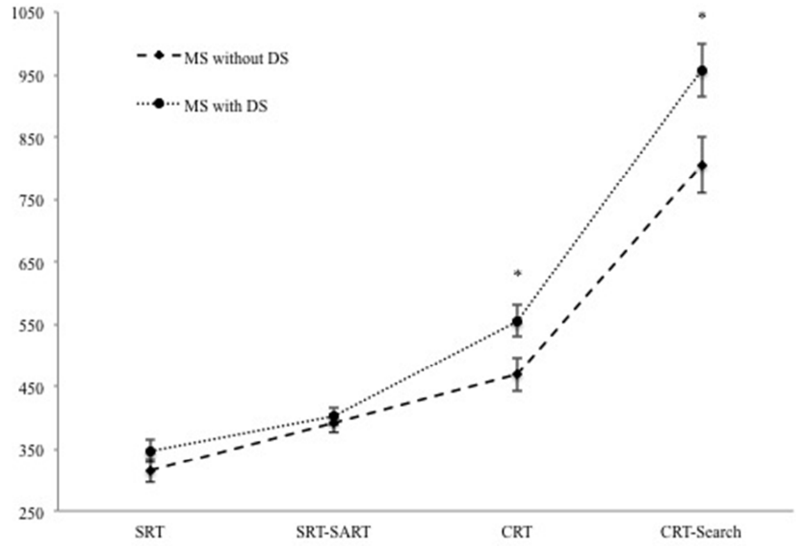

201x107mm (75 x 75 DPI)



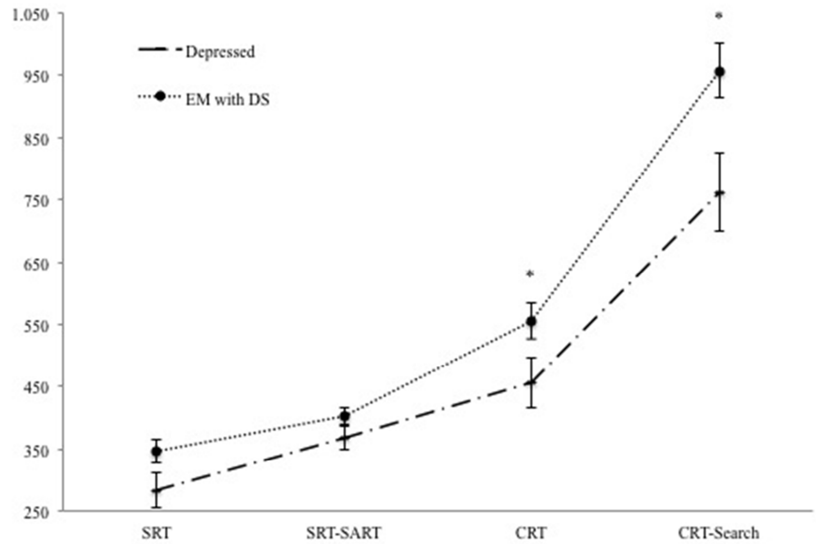

210x119mm (72 x 72 DPI)




212x118mm (72 x 72 DPI)




211x119mm (72 x 72 DPI)




211x119mm (72 x 72 DPI)